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Title:
AMINOPHENYL PYRIMIDONE DERIVATIVES

Abstract:

The invention relates to a pyrimidone derivative represented by formula (I) or a salts thereof, wherein: n is 0 or 1, W represents a bond, a carbonyl group -C(O)- or a sulfonyl group -S(O)2-; when W represents a carbonyl group -C(O)- then R1 represents a hydrogen atom, a C1-16 alkyl group which may be substituted, a C6,10 aryl group which may be substituted or a heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, having total ring-constituting atoms of 5-10 and being optionally substituted, when W represents a sulfonyl group -S(O)2-, R<1> represents a C1-6 alkyl group which may be substituted, a C6,10 aryl group which may be substituted or a heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, having total ring-constituting atoms of 5-10 and being optionally substituted; when W represents a bond then n is 0 and R1 represents a hydrogen atom or a C1-6 alkyl group, R2 represents a hydrogen atom or a C1-6 alkyl group which may be substituted by an optionally substituted phenyl group; and R3 represents a pyridyl ring optionally substituted by a C1-4 alkyl group, C1-4 alkoxy group or a halogen atom. The invention relates also to a medicament comprising the said derivative or a salt thereof as an active ingredient which is used for preventive and/or therapeutic treatment of a neurodegenerative disease caused by abnormal activity of GSK3 beta , such as Alzheimer's disease.

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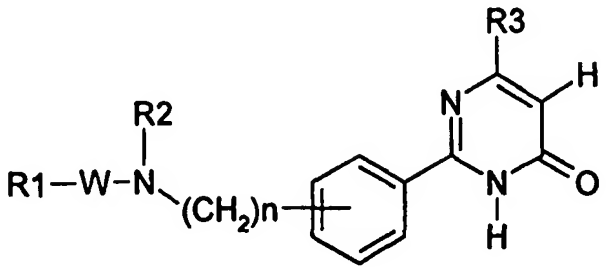
(54) Title: AMINOPHENYL PYRIMIDONE DERIVATIVES



(I)

(57) Abstract: The invention relates to a pyrimidone derivative represented by formula (I) or a salts thereof, wherein: n is 0 or 1, W represents a bond, a carbonyl group -C(O)- or a sulfonyl group -$S(O)_2$-; when W represents a carbonyl group -C(O)- then R_1 represents a hydrogen atom, a C_{1-16} alkyl group which may be substituted, a $C_{6,10}$ aryl group which may be substituted or a heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, having total ring-constituting atoms of 5-10 and being optionally substituted, when W represents a sulfonyl group -$S(O)_2$-, R^1 represents a C_{1-6} alkyl group which may be substituted, a $C_{6,10}$ aryl group which may be substituted or a heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, having total ring-constituting atoms of 5-10 and being optionally substituted; when W represents a bond then n is 0 and R_1 represents a hydrogen atom or a C_{1-6} alkyl group, R2 represents a hydrogen atom or a C_{1-6} alkyl group which may be substituted by an optionally substituted phenyl group; and R3 represents a pyridyl ring optionally substituted by a C_{1-4} alkyl group, C_{1-4} alkoxy group or a halogen atom. The invention relates also to a medicament comprising the said derivative or a salt thereof as an active ingredient which is used for preventive and/or therapeutic treatment of a neurodegenerative disease caused by abnormal activity of GSK3β, such as Alzheimer's disease.

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SPECIFICATION

AMINOPHENYL PYRIMIDONE DERIVATIVES

Technical Field

The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal activity of GSK3β.

Background Art

GSK3β (glycogen synthase kinase 3β) is a proline directed serine, threonine kinase that plays an important role in the control of metabolism, differentiation and survival. It was initially identified as an enzyme able to phosphorylate and hence inhibit glycogen synthase. It was later recognized that GSK3β was identical to tau protein kinase 1 (TPK1), an enzyme that phosphorylates tau protein in epitopes that are also found to be hyperphosphorylated in Alzheimer's disease and in several taupathies.

Interestingly, protein kinase B (AKT) phosphorylation of GSK3β results in a loss of its kinase activity, and it has been hypothesized that this inhibition may mediate some of the effects of neurotrophic factors. Moreover, phosphorylation by GSK3β of β-catenin, a protein involved in cell survival, results in its degradation by an ubiquitinilation dependent proteasome pathway.

Thus, it appears that inhibition of GSK3β activity may result in neurotrophic activity. Indeed there is evidence that lithium, an uncompetitive inhibitor of GSK3β, enhances neuritogenesis in some models and also increases neuronal survival, through the induction of survival factors such as Bcl-2 and the inhibition of the expression of proapoptotic factors such as P53 and Bax.

Recent studies have demonstrated that β-amyloid increases the GSK3β activity and tau protein phosphorylation. Moreover, this hyperphosphorylation as well as the neurotoxic effects of β-amyloid are blocked by lithium chloride and by a GSK3β antisense mRNA. These observations strongly suggest that GSK3β may be the link between the two major pathological processes in Alzheimer's disease : abnormal APP (Amyloid Precursor Protein) processing and tau protein hyperphosphorylation.

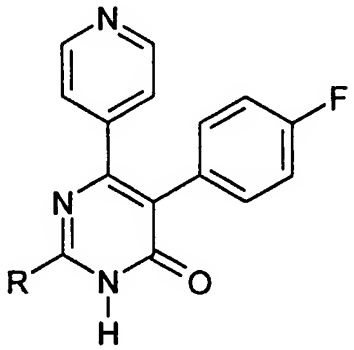
Although tau hyperphosphorylation results in a destabilization of the neuronal cytoskeleton, the pathological consequences of abnormal GSK3β activity are,

most likely, not only due to a pathological phosphorylation of tau protein because, as mentioned above, an excessive activity of this kinase may affect survival through the modulation of the expression of apoptotic and antiapoptotic factors. Moreover, it has been shown that β-amyloid-induced increase in GSK3β activity results in the phosphorylation and, hence the inhibition of pyruvate dehydrogenase, a pivotal enzyme in energy production and acetylcholine synthesis.

Altogether these experimental observations indicate that GSK3β may find application in the treatment of the neuropathological consequences and the cognitive and attention deficits associated with Alzheimer's disease, as well as other acute and chronic neurodegenerative diseases. These include, in a non-limiting manner, Parkinson's disease, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma.

In addition GSK3β may find application in the treatment of other diseases such as: Non-insulin dependent diabetes (such as diabetes type II) and obesity; manic depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

PCT application WO 98/24782 discloses compounds represented by the following formula (A):



(A)

wherein R represents a 2,6-dichlorobenzyl group, a 2-(2-chlorophenyl)ethylamino

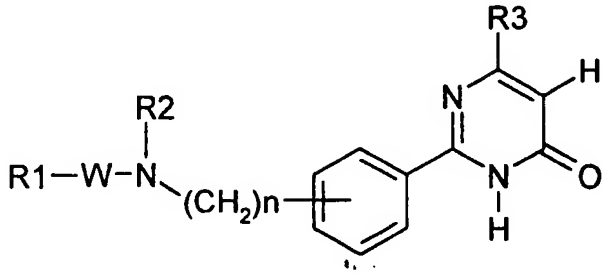
group, a 3-phenylpropylamino group, or a 1-methyl-3-phenylpropylamino group. The compounds represented by formula (A) are characterized by a 4-fluorophenyl group at the 5-position of the pyrimidine ring. The main pharmacological activity disclosed for the compounds represented by formula (A) is an anti-inflammatory effect, whereas the compounds of the present invention represented by formula (I) herein below are useful as GSK3β inhibitors or as medicaments for the therapeutic treatment of neurodegenerative diseases, and therefore, their pharmacological activities are totally different.

Disclosure of the Invention

An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables prevention and/or treatment of the neurodegenerative diseases such as Alzheimer's disease.

Thus, the inventors of the present invention have identified compounds possessing inhibitory activity against GSK3β. As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases.

The present invention thus provides pyrimidone derivatives represented by formula (I) or salts thereof, solvates thereof or hydrates thereof:



(I)

wherein:

n is 0 or 1,

W represents a bond, a carbonyl group –C(O)- or a a sulfonyl group $–S(O)_2-$;

* When W represents a carbonyl group –C(O)- then R_1 represents a hydrogen atom, a C_{1-6} alkyl group which may be substituted, a $C_{6,10}$ aryl group which may be substituted or a heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, having total ring-constituting atoms of 5-10 and being optionally substituted,

* When W represents a sulfonyl group $–S(O)_2-$, R_1 represents a C_{1-6} alkyl group which may be substituted, a $C_{6,10}$ aryl group which may be substituted or a heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, having total ring-constituting atoms of 5-10 and being optionally substituted;

* When W represents a bond then n is 0 and R_1 represents a hydrogen atom or a C_{1-6} alkyl group,

R2 represents a hydrogen atom or a C_{1-6} alkyl group which may be substituted by an optionally substituted phenyl group; and

R3 represents a pyridyl ring optionally substituted by a C_{1-4} alkyl group, C_{1-4} alkoxy group or a halogen atom.

According to another aspect of the present invention, there is provided a medicament comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives represented by formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof. As preferred embodiments of the medicament, there are provided the aforementioned medicament which is used for preventive and/or therapeutic treatment of diseases caused by abnormal GSK3β activity, and the

aforementioned medicament which is used for preventive and/or therapeutic treatment of neurodegenerative diseases and in addition other diseases such as: Non-insulin dependent diabetes (such as diabetes type II) and obesity; manic depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

As further preferred embodiments of the present invention, there are provided the aforementioned medicament wherein the diseases are neurodegenerative diseases and are selected from the group consisting of Alzheimer's disease, Parkinson's disease, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma, and the aforementioned medicament in the form of pharmaceutical composition containing the above substance as an active ingredient together with one or more pharmaceutical additives.

The present invention further provides an inhibitor of GSK3β activity comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the salts thereof, and the solvates thereof and the hydrates thereof.

According to further aspects of the present invention, there are provided a method for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal GSK3β activity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof; and a use of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof for the manufacture of the aforementioned medicament.

As used herein, the C_{1-6} alkyl group represents a straight or branched alkyl group having 1 to 6 carbon atoms, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, and the like;

The C_{1-6} alkoxy group represents an alkyloxy group having 1 to 6 carbon atoms, for example, methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, pentyloxy group, isopentyloxy group, neopentyloxy group, 1,1-dimethylpropyloxy group and the like;

The halogen atom represents a fluorine, chlorine, bromine or iodine atom;

The C_{1-2} perhalogenated alkyl group represents an alkyl group wherein all the hydrogen have been substituted by a halogeno, for example a CF_3 or C_2F_5,

The C_{1-3} halogenated alkyl group represents an alkyl group wherein at least one hydrogen has not been substituted by a halogeno;

The C_{1-6} monoalkylamino group represents an amino group substituted by one C_{1-5} alkyl group, for example, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group and isopentylamino group;

The C_{2-12} dialkylamino group represents an amino group substituted by two C_{1-5} alkyl groups, for example, dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group and diisopropylamino group;

The $C_{6,10}$ aryl group represents a phenyl group, 1-naphthyl group, 2-naphthyl group, and tetrahydronaphtyl group;

The C_{1-6} alkylthio and $C_{6,10}$ arylthio represent respectively a thiol substituted by a C_{1-6} alkyl or $C_{6,10}$ aryl;

The heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5-10 (or [heterocyclic ring]) represents a furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, furopyridin ring, isobenzofuran ring, chromene ring, chroman ring, isochroman ring, thiophene ring, benzothiophene ring, thienopyridyne ring, pyrrole ring, pyrroline ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, imidazopyridine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indolizine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzimidazole ring, purine ring, quinolizine ring, quinoline ring, phthalazine ring, naphtylidine ring, quinoxaline ring,

quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, thiazole ring, benzothiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, dioxane ring, dithian ring, morpholine ring, thiomorpholine ring, phthalimide ring and the like.

In the definition of R1, when the C_{1-6} alkyl group or the group $C_{6,10}$ aryl group are substituted they can be substituted by one to three substituents selected from :

a halogen atom, a hydroxyl function, a nitro group, a cyano group,
a C_{1-6} alkyl group,
a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group,
a C_{1-6} alkoxy group, a $C_{6,10}$ aryloxy group, a methylenedioxy group,
a C $_{1-6}$ alkylthio group, a $C_{6,10}$ arylthio group, a pyridylthio group,
a formyl group, carboxy group, a C_{1-6} alkoxycarbonyl group,
a C_{1-6} alkylcarbonyl group, a $C_{6,10}$ arylcarbonyl group, a benzylcarbonyl group,
a (piperidin-1-yl)carbonyl group, a (morpholin-1-yl)carbonyl group, a morpholin-1-yl-amino,
a [4-(4-acetylphenyl)-piperazin-1-yl]carbonyl group,
a benzylaminocarbonyl group,
a [heterocyclic ring]-C_{1-6} alkylaminocarbonyl group,
a C_{1-6} alkylcarbonylamino group, a $C_{6,10}$ arylcarbonylamino group,
an amino, a C_{1-6} monoalkylamino group, C_{2-12} dialkylamino group,
a C_{1-6} alkoxycarbonylamino group,
a phenyl group which may be substituted and a [heterocyclic ring] which may be substituted.

When a phenyl group as a substituent or a [heterocyclic ring] are substituted, they can have one to three substituents selected from the group consisting of :

a halogen atom, a hydroxyl function, a nitro group, a cyano group,
a C_{1-6} alkyl group,
a C_{1-2} perhalogenated alkyl group, a C_{1-3} halogenated alkyl group,
a C_{1-6} alkoxy group, a $C_{6,10}$ aryloxy group, a methylenedioxy group,
a C $_{1-6}$ alkylthio group, a $C_{6,10}$ arylthio group, a pyridylthio group,
a formyl group, a carboxy group, a C_{1-6} alkoxycarbonyl group,
a C_{1-6} alkylcarbonyl group, a $C_{6,10}$ arylcarbonyl group, a benzylcarbonyl group,
a [heterocyclic ring]-C_{1-6} alkylaminocarbonyl group,
a C_{1-6} alkylcarbonylamino group, a $C_{6,10}$ arylcarbonylamino group,
an amino, a C_{1-6} monoalkylamino group, C_{2-10} dialkylamino group,
a C_{1-6} alkoxycarbonylamino group.

The compounds represented by the aforementioned formula (I) may form a salt. Examples of the salt include, when an acidic group exists, salts of alkali metals and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)aminomethane, N,N-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, N-methylglucamine, and L-glucamine; or salts with basic amino acids such as lysine, δ-hydroxylysine, and arginine. The base-addition salts of acidic compounds are prepared by standard procedures well known in the art.

When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid, glycolic acid, glucuronic acid, ascorbic acid, nicotinic acid, and salicylic acid; or salts with acidic amino acids such as aspartic acid, and glutamic acid.

The acid-addition salts of the basic compounds are prepared by standard procedures well know in the art which include, but are not limited thereto, dissolving the free base in an aqueous alcohol solution containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and an acid in an organic solvent, in which case the salt separates directly, or is precipitated with a second organic solvent, or can be obtained by concentration of the solution. The acids which can be used to prepare the acid-addition salts include preferably those which produce, when combined with the free base, pharmaceutically-acceptable salts, that is, salts whose anions are relatively innocuous to the animal organism in pharmaceutical doses of the salts, so that the beneficial properties inherent in the free base are not compromised by side effects ascribable to the anions. Although medicinally acceptable salts of the basic compounds are preferred, all acid-addition salts are within the scope of the present invention.

In addition to the pyrimidone derivatives represented by the aforementioned formula (I) and salts thereof, their solvates and hydrates also fall within the scope of the present invention. The pyrimidone derivatives represented by the aforementioned formula (I) may have one or more asymmetric carbon

atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R) and (S) configuration, and the pyrimidone derivative may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers in pure form, any mixtures of stereoisomers, racemates and the like fall within the scope of the present invention.

Furthermore, as the pyrimidone derivatives represented by the aforementioned formula (I), a 3H-4-one compound, a 4-hydroxy compound, and a 1H-4-one compound may exist as tautomers. The existence of such tautomers is readily apparent to those skilled in the art, and these tautomers fall within the scope of the present invention.

Examples of preferred compounds of the present invention are shown in table 1 thereafter. However, the scope of the present invention is not limited by these compounds.

Preferred compounds of the present invention represented by formula (I) include also:

(1) Compounds wherein R3 represents a 3- or 4-pyridyl group and more preferably 4-pyridyl group, which may be substituted by a C_{1-2} alkyl, group, C_{1-2} alkoxy group or a halogen atom.

More preferred compounds of the present invention represented by formula (I) include also:

(1) Compounds wherein R3 represents an unsubstituted 4-pyridyl group.
(2) Compounds wherein W represents a sulfonyl group $-S(O)_2-$.
(3) Compounds wherein W represents a carbonyl group –C(O)-.
(4) Compounds wherein R3 is defined under (1) and W under (2).
(5) Compounds wherein R3 is defined under (1) and W under (3).

Particularly preferred compounds of the present invention represented by formula (I) include also :

2-(4-(pyrid-2-yl-acetyl-amino))phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one,
2-(3-(phenylmethylsulfonylamino)phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one,
2-(4-(5'-methoxy-5'-oxo-valeryl-amino)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one,
2-(4-(5'-hydroxy-5'-oxo-valeryl-amino)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one,
2-(4-(5'-piperid-1-yl-5'-oxo-valeryl-amino)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one,

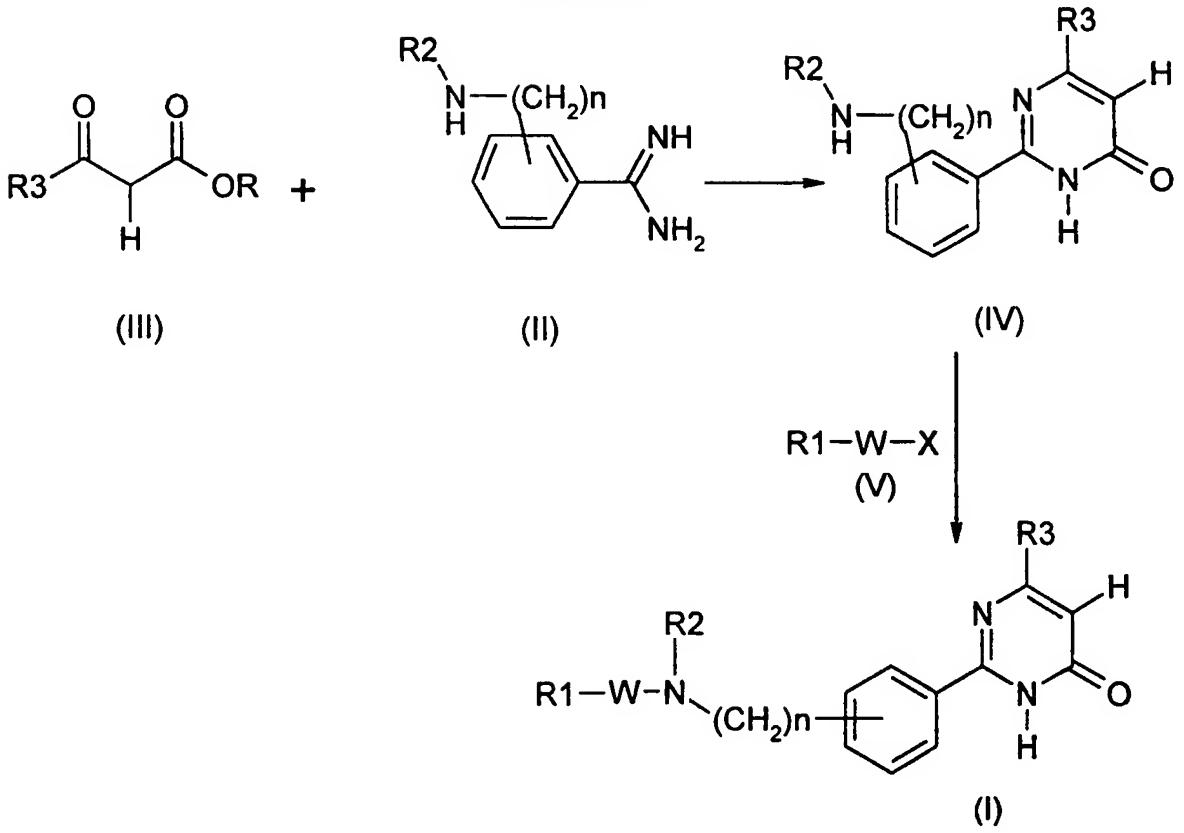
2-(4-(chloroacetyl-amino)phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one,
2-(4-(4'-methyl-piperazin-1-yl-acetyl-amino)phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one,
2-(4-(4'-methoxy-4'-oxo-butyryl-aminomethyl)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one, and
2-(4-(4'-hydroxy-4'-oxo-butyryl-aminomethyl)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one.

As a further object, the present invention concerns also methods for preparing the pyrimidone compounds represented by the aforementioned formula (I).

These compounds can be prepared, for example, according to methods explained below.

1. Preparation method

scheme 1



(In the above scheme, R represents an alkyl group, which may be substituted, and definitions of R1 to R3 are the same as those already described.)

The 3-ketoester represented by the above formula (III) is allowed to react with the compound represented by formula (II) or a salt thereof to obtain the compound of formula (IV) in the presence of a base such as lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, 1,8-diazabicyclo[5,4,0]undec-7-ene, triethylamine, diisopropyl-ethylamine, dimethylbenzylamine, dimethylaniline, diethylaniline and the like.

Examples of a solvent suitable for the reaction include, for example, alcoholic solvent such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbon solvents such as benzene, toluene, xylene; halogenated solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide

methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide and the like. Generally, a single solvent or a mixture of two or more solvents may be used depending on the base used, and the reaction may be carried out for 1 hour to 14 days at a suitable temperature ranging from 0° to 250°C under nitrogen or argon atmosphere or in ordinary air.

The compounds of formula (IV) is then allow to react with an appropriate activated acid derivative or a sulfonylhalide of formula (V), to obtain the compounds of formula (I).

For example when W is a carbonyl group, the reaction may be carried out with an appropriate acid halide of formula (V) wherein X represents a halide in a solvent such as for example tetrahydrofuran, dimethylformamide, in a presence of a base such as triethylamine, pryridine, dimethylaminopyridine, at a suitable temperature ranging from 20°C to reflux temperature. Or the reaction may be carried out in a presence of a coupling agent such as for example 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, dicyclohexylcarbodiimide in a solvent such as for example tetrahydrofuran, dimethylformamide, in a presence of a base such as triethylamine, pryridine, dimethylaminopyridine, at a suitable temperature ranging from 20°C to reflux temperature.

When W is a sulfonyl group the reaction may be carried out with sulfonyl halide of formula (V) wherein X represents a halide in a solvent such as for example tetrahydrofuran, dimethylformamide, in a presence of a base such as triethylamine, pyridine, dimethylaminopyridine, at a suitable temperature ranging from 20°C to reflux temperature.

When W is a bond the reaction may be carried out with a halide derivative of formula (V) wherein X represents a halide in a solvent such as for example tetrahydrofuran, dimethylformamide, in a presence of a base such as triethylamine, pyridine, dimethylaminopyridine, at a suitable temperature ranging from 20°C to reflux temperature.

Compounds of formula (II), (III) and formula (IV) are commercially available or may be synthesized according to known methods of one skilled in the art.

For example compounds of formula (III), wherein R3 represent a 4-pyridyl group

optionally substituted by a C_{1-4} alkyl group, C_{1-4} alkoxy group or a halogen atom, can be prepared by reacting a nicotinic acid optionally substituted by a C_{1-4} alkyl group, C_{1-4} alkoxy group or an halogen, with a malonic acid monoester. The reaction can be carried out using methods well known methods to one skilled in the art, such as for example in presence of a coupling agent such as 1,1'-carbonylbis-1H-imidazole in a solvent such as a tetrahydrofuran at a temperature ranging from 20 to 70°C.

In the above reactions protection or deprotection of a functional group may sometimes be necessary. A suitable protecting group can be chosen depending on the type of a functional group, and a method described in the literature may be applied. Examples of protecting groups, of protection and deprotection methods are given for example in *Protective groups in Organic Synthesis* Greene et al., 2nd Ed. (John Wiley & Sons, Inc., New York).

In addition when applicable, compound of formula (I) could be derivatised into other compound of formula (I), using well known methods in the art.

The compounds of the present invention have inhibitory activity against GSK3β. Accordingly, the compounds of the present invention are useful as an active ingredient for the preparation of a medicament, which enables preventive and/or therapeutic treatment of neurodegenerative diseases such as Alzheimer's disease. In addition, the compounds of the present invention are also useful as an active ingredient for the preparation of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases such as Parkinson's disease, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma; and other diseases such as non-insulin dependent diabetes (such as diabetes type II) and obesity; manic depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

The present invention further relates to a method for treating neurodegenerative diseases caused by abnormal activity of GSK3β and of the aforementioned diseases which comprises administrating to a mammalian

organism in need thereof an effective amount of a compound of the formula (I).

As the active ingredient of the medicament of the present invention, a substance may be used which is selected from the group consisting of the compound represented by the aforementioned formula (I) and pharmacologically acceptable salts thereof, and solvates thereof and hydrates thereof. The substance, per se, may be administered as the medicament of the present invention, however, it is desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more of pharmaceutical additives. As the active ingredient of the medicament of the present invention, two or more of the aforementioned substances may be used in combination. The above pharmaceutical composition may be supplemented with an active ingredient of another medicament for the treatment of the above mentioned diseases. A type of the pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or parenteral administration. For example, the pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations such as in the form of lyophilized preparations, and may be used by dissolving just before use in an appropriate aqueous medium such as physiological saline. Sustained-release preparations such as those coated with a polymer may be directly administered intracerebrally.

Types of pharmaceutical additives used for the manufacture of the pharmaceutical composition, content ratios of the pharmaceutical additives relative to the active ingredient, and methods for preparing the pharmaceutical composition may be appropriately chosen by those skilled in the art. Inorganic or organic substances, or solid or liquid substances may be used as pharmaceutical additives. Generally, the pharmaceutical additives may be incorporated in a ratio ranging from 1% by weight to 90% by weight based on the weight of an active ingredient.

Examples of excipients used for the preparation of solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. For the preparation of liquid compositions for oral administration, a conventional inert diluent such as water or a vegetable oil may be used. The liquid composition may contain, in addition to the inert diluent, auxiliaries such as moistening agents, suspension aids, sweeteners, aromatics, colorants, and preservatives. The liquid composition may be filled in capsules made of an absorbable material such as gelatin. Examples of solvents or suspension mediums used for the preparation of compositions for parenteral administration, e.g. injections, suppositories, include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of base materials used for suppositories include, for example, cacao butter, emulsified cacao butter, lauric lipid, witepsol.

Dose and frequency of administration of the medicament of the present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a disease and the like. Generally, a daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient), and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the medicament is used as an injection, administrations may preferably be performed continuously or intermittently in a daily dose of 0.001 to 100 mg (the weight of an active ingredient) to an adult.

Chemical Examples

The present invention will be explained more specifically with reference to examples. However, the scope of the present invention is not limited to the following examples.

Example 1 : 2-(4-aminophenyl)-6-(4-pyridyl)-pyrimidin-4-one

To a solution of 2.6g (13.5mMoles) 3-oxo-3-(pyrid-4-yl)propionate in 50 ml absolute ethanol in a 250 ml round bottom flask, fitted with a condenser, is added 2.32g (13.5m moles) of 4-amino benzamidine hydrochloride, followed by 8.8 ml of a 21% sodium ethanolate solution in ethanol. The obtained suspension is refluxed for 18h. After cooling down, the reaction is stopped by adding 2ml acetic acid. The compound is precipitated by addition of 2 volumes water, the solid is filtered and successively washed with water, ethyl acetate then ether, to give 2.2 g of a pale yellow solid (62%).

Example 2 : 2-(4-(pyrid-2-yl-acetyl-amino))phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one

To a suspension of 2-(4-aminophenyl)-6-(pyrid-4-yl)-pyrimidin-4-one in 4ml dimethylformamide (DMF) are added successively: 62mg of 1-hydroxybenzotriazole hydrate (0.4mMole), 97mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.5mMole), 20mg of 4-dimethylaminopyridine and 70mg of 2-pyridyl-acetic acid (0.4mMole). The obtained suspension is heated 1h at 50°C, and is then stirred for 18h at room temperature. The compound is precipitated by addition of 20ml water and separated by filtration. The obtained solid is washed with water then ether, to obtain 38.5mg of a white solid (50%).

Example 3 : 2-(3-(benzylsulfonylamino)phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one

To a suspension of 53mg 2-(3-aminophenyl)-6-(pyrid-4-yl)-pyrimidin-4-one (0.2mMole) in 3ml of a tetrahydrofuran (THF)/pyridine 50/50 mixture 76mg of α-toluenesulphonyl chloride is added. The mixture is heated 7h at 50°C and then stirred for 48h at room temperature. The reaction is stopped by addition of 10ml water. The precipitate is separated by filtration and washed successively with water, ethyl acetate then ether, to obtain 55mg of a clear solid (65%).

Example 4 : 2-(4-(5'-methoxy-5'-oxo-valeryl-amino)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one

To a solution of 1.06g 2-(4-aminophenyl)-6-(pyrid-4-yl)-pyrimidin-4-one (4mMole) in 60ml DMF/pyridine (40/20) mixture 790mg of methyl-5-chloro-5-oxovalerate (0.48mMole) is added. The mixture is heated 3h at 50°C then stirred 48h at room temperature. The reaction is stopped by addition of 3 volumes water. The obtained precipitate is separated by filtration and washed successively with water, ethyl acetate and ether, to obtain 1.32g of a beige solid (84%) of 2-(4-(5'-methoxy-5'-oxo-valeryl-amino)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one

Example 5 : 2-(4-(5'-hydroxy-5'-oxo-valeryl-amino)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one

To a suspension of 650mg 2-(4-(5'-methoxy-5'-oxo-valeryl-amino)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one (1.65mMole) in 50ml THF/H_20 40/10 mixture is added 125mg LiOH (3.0mMole). The solution is stirred 48h at room temperature. The THF is evaporated under reduced pressure, and the solution is neutralized with solution of HCl 1N. The formed precipitate is separated by filtration and washed successively with water, ethyl acetate and ether, to obtain 550mg of a beige solid (88%).

Example 6 : 2-(4-(5'-piperid-1-yl-5'-oxo-valeryl-amino)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one

To a suspension of 76mg 2-(4-(5'-hydroxy-5'-oxo-valeryl-amino)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one (0.2mMoles) in 3ml anhydrous DMF is added successively : 62mg of 1-hydroxybenzotriazole hydrate (0.4mMole), 96mg of 1-(3-dimethylaminopropyl)-3- ethylcarbodiimide hydrochloride (0.5mMole), 10mg of 4-dimethylaminopyridine and 100µl piperidine (1mMole). The suspension is heated 2h à 50°C, then stirred for18h at room temperature. The solvent is evaporated under reduced pressure and the residue is taken up in 54ml water. The formed precipitate is separated by filtration and washed successively with water, ethyl acetate and ether, to obtain 55mg of a solid (62%).

Example 7 : 2-(4-(chloroacetyl-amino)phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one

To a suspension de 2-(4-aminophenyl)-6-(pyrid-4-yl)-pyrimidin-4-one (465mg, 1,76mmoles) in DMF (50mL) is added successively 845 mg of 1-(3-dimethylaminopropyl)-3- ethylcarbodiimide hydrochloride (4,4mmoles) and 35 mg 4-dimethylaminopyridine (0,26mmoles).
The solution is stirred for 20h at room temperature. The solvent is evaporated under reduced pressure, and the residue is triturated in water. The formed precipitate is separated by filtration and washed successively with water, ethyl acetate and ether, to obtain 530mg of a solid (88%).

Example 8 : 2-(4-(4'-methyl-piperazin-1-yl-acetyl-amino)phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one

A solution of 85mg 2-(4-(chloroacetyl-amino)phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one (0.25mmoles) and 140µL 1-méthylpipérazine (1,25mmoles) in DMF is stirred for 3h at room temperature. The solvent is evaporated under reduced pressure, and the residue is triturated in water. The formed precipitate is separated by filtration and washed successively with water, ethyl acetate and ether, to obtain 36mg of a solid (36%).

Example 9 : 2-(4-(4'-methoxy-4'-oxo-butyryl-aminomethyl)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one

To a solution of 5.4g (17.4mMoles) 4-amino benzamidine hydroacetate in 175 ml anhydrous DMF and 50 ml dimethylsulfoxide (DMSO) in a 1L round bottom flask, fitted with a condenser, is added 5.42 ML DBU (34.8 mMoles), followed by 4.04g (20.9mmoles) 3-oxo-3-(pyrid-4-yl)propionate. The obtained mixture is refluxed for 18h. After cooling down, the reaction is stopped by adding 7ml acetic acid The solvent is evaporated under reduced pressure, and the residue is triturated in water The solid is filtered and successively washed with water, ethyl acetate then ether, to give 5.4 g of a pale yellow solid (82%). The obtained derivative (5.1 g, 13.4 mMoles) is taken up in CH_2Cl_2, cooled to 0°C and 71 ml of TFA is added dropwise. The mixture is stirred for 1h at room temperature, and the solvent is evaporated under reduced pressure. The residue is triturated in EtOAc, filtered, washed succesively with EtOAc and ether, to afford 6.5 g of a beige solid (96%)

To a solution of 506 mg 2-(4-aminomethyl-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one,

dihydrotrifluoroacetate (1mMole) in 15ml DMF is added 350µL (2 mMoles) of Diisopropyl ethyl amine, and the solution is stirred for 5 min at room temperature. A preformed solution of 280 mg methylsuccinate (2 mMoles) and 370 mg carbonyldiimidazole (2.2 mMoles) in 5 ml CH_2Cl_2 is added dropwise.. The mixture is stirred for 1h30 at room temperature. The reaction is stopped by addition of 3 volumes water. The obtained precipitate is separated by filtration and washed successively with water, ethyl acetate and ether, to obtain 244 mg of a beige solid (62%)to give 2-(4-(4'-methoxy-4'-oxo-butyryl-aminomethyl)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one

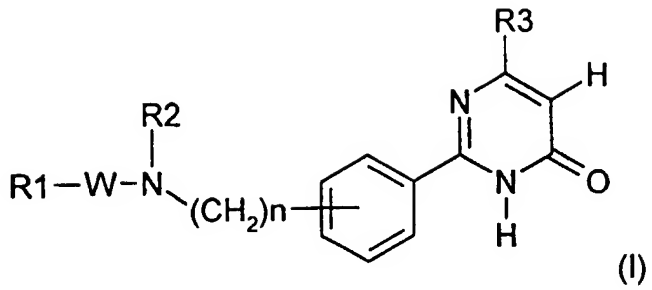
Example 10 : 2-(4-(4'-hydroxy-4'-oxo-butyryl-aminomethyl)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one

To a suspension of 200mg 2-(4-(4'-methoxy-4'-oxo-butyryl-aminomethyl)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one (0.5mMole) in 35ml THF/H_20 70/30 mixture is added 62.3mg LiOH (2.5mMole). The solution is stirred 1h at room temperature. The THF is evaporated under reduced pressure, and the solution is neutralized with a solution of HCl 1N. The formed precipitate is separated by filtration and washed successively with water, ethyl acetate and ether, to obtain 175mg of a beige solid (88%).

Table 1 lists chemical structure and physical data of compounds of the aforementioned formula (I). These compounds have been prepared according methods described here above.

In table 1, R3 is a 4-pyridyl group.

Table 1



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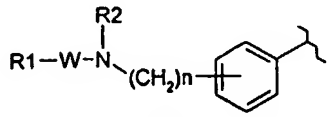

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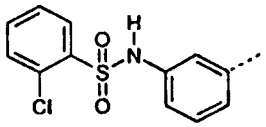
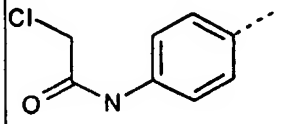
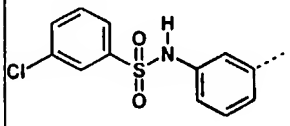
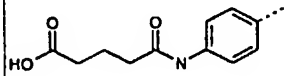
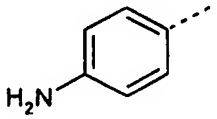
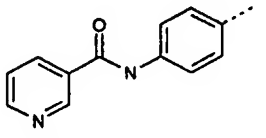
1		439
2		341
3		439
4		379
5		265
6		370
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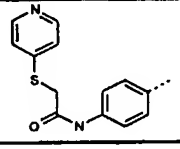
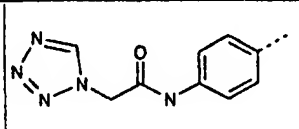
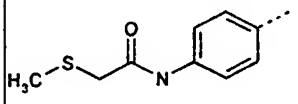
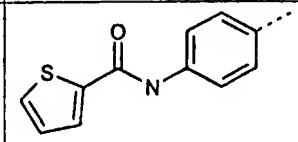
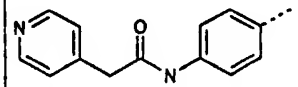
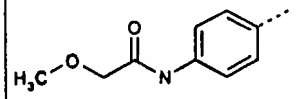
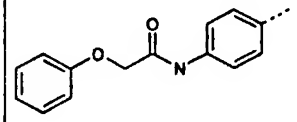
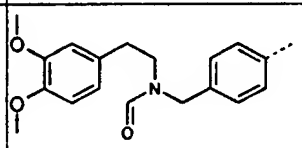
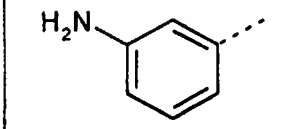
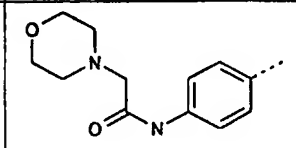
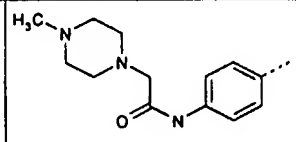
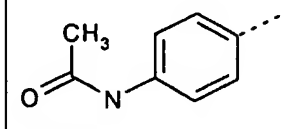
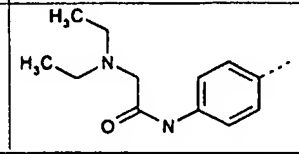
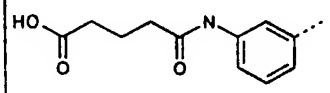
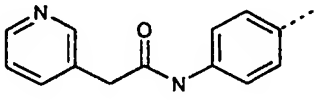
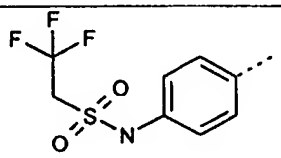
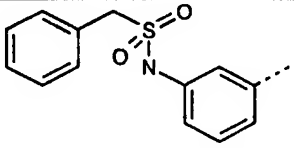
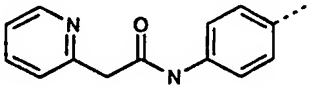
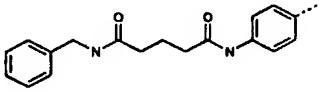
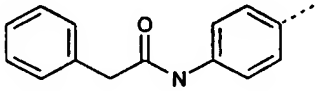
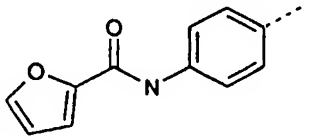
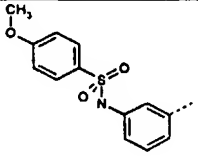
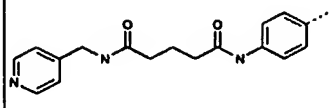
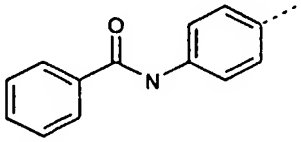
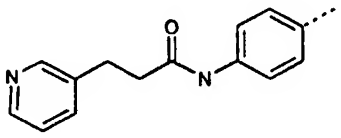
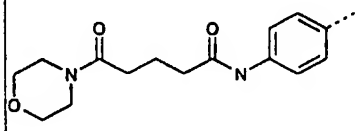
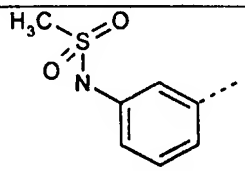
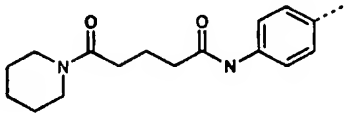
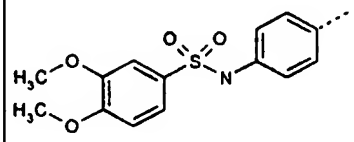
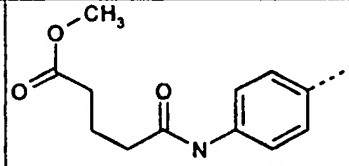
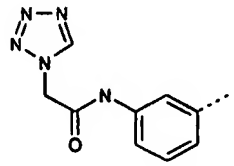
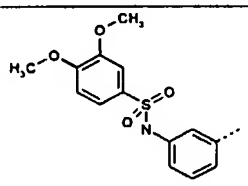
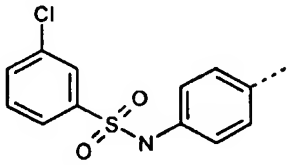
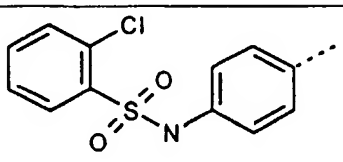
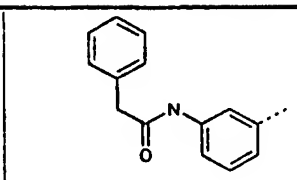
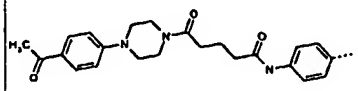
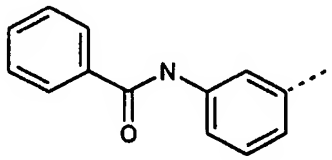
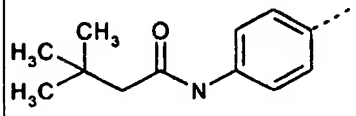
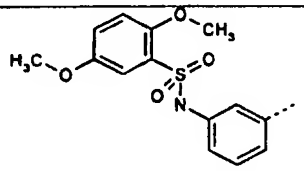
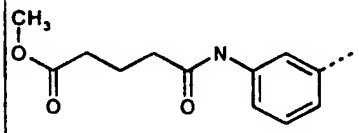
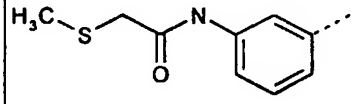
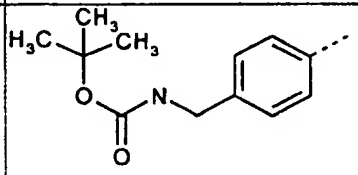
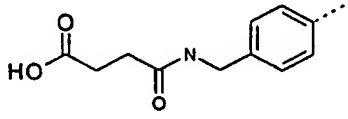
8		416

9		375
10		353
11		375
12		384
13		337
14		399
15		471
16		265
17		392
18		405
19		307
20		378

21		379
22		384
23		411
24		419
25		384
26		468
27		383
28		359
29		435
30		469
31		369

32		398
33		448
34		323
35		446
36		465
37		393
38		375
39		465
40		439
41		439

42		383
43		565
44		369
45		363
46		465
47		393
48		353
49		379
50		379

Test Example: Inhibitory activity of the medicament of the present invention against GSK3β:

Two different protocols can be used.

In a first protocol : 7.5 µM of prephosphorylated GS1 peptide and 10 µM ATP (containing 300,000 cpm of 33P-ATP) were incubated in 25 mM Tris-HCl, pH 7.5, 0.6 mM DTT, 6 mM $MgCl_2$, 0.6 mM EGTA, 0.05 mg/ml BSA buffer for 1 hour at room temperature in the presence of GSK3β (total reaction volume : 100 microliters).

In a second protocol : 4.1 µM of prephosphorylated GS1 peptide and 42 µM ATP (containing 260,000 cpm 33P-ATP) were incubated in 80 mM Mes-NaOH, pH 6.5, 1 mM Mg acetate, 0.5 mM EGTA, 5 mM 2-mercaptoethanol, 0.02% Tween 20, 10% glycerol buffer for 2 hours at room temperature in the presence of GSK3β. Inhibitors were solubilised in DMSO (final solvent concentration in the reaction medium, 1%).

The reaction was stopped with 100 microliters of a solution made of 25 g polyphosphoric acid (85% P_2O_5), 126 ml 85% H_3PO_4, H_2O to 500 ml and then diluted to 1 :100 before use. An aliquot of the reaction mixture was then transferred to Whatman P81 cation exchange filters and rinsed with the solution described above. Incorporated 33P radioactivity was determined by liquid scintillation spectrometry.
The phosphorylated GS-1 peptide had the following sequence :
NH2-YRRAAVPPSPSLSRHSSPHQS(P)EDEE-COOH.

The GSK3β inhibitory activity of the compounds of the present invention are expressed in IC_{50}, and as an illustration the range of IC_{50}'s of the compounds given in table 1 is between 0.03 to 3 micromolar concentrations.

Formulation Example

(1) Tablets

The ingredients below were mixed by an ordinary method and compressed by using a conventional apparatus.

Compound of Example 1	30 mg
Crystalline cellulose	60 mg
Corn starch	100 mg
Lactose	200 mg
Magnesium stearate	4 mg

(2) Soft capsules

The ingredients below were mixed by an ordinary method and filled in soft capsules.

Compound of Example 1	30 mg
Olive oil	300 mg
Lecithin	20 mg

(1) Parenteral preparations

The ingredients below were mixed by an ordinary method to prepare injections contained in a 1 ml ample.

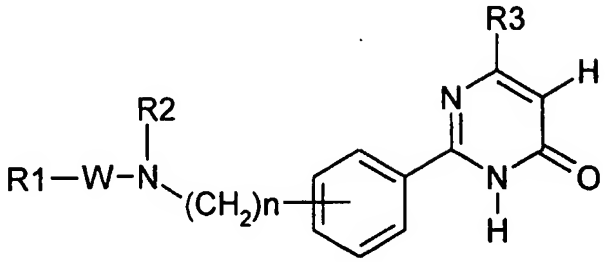
Compound of Example 1	3 mg
Sodium chloride	4 mg
Distilled water for infection	1 ml

Industrial Applicability

The compounds of the present invention have GSK3β inhibitory activity and are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal activity of GSK3β .

What is claimed is:

1. A pyrimidone derivative represented by formula (I) or a salts thereof, or a solvate thereof or a hydrate thereof:



(I)

wherein:

n is 0 or 1,

W represents a bond, a carbonyl group –C(O)- or a a sulfonyl group $-S(O)_2-$;

* When W represents a carbonyl group –C(O)- then R_1 represents a hydrogen atom, a C_{1-6} alkyl group which may be substituted, a $C_{6,10}$ aryl group which may be substituted or a heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, having total ring-constituting atoms of 5-10 and being optionally substituted,

* When W represents a sulfonyl group $-S(O)_2-$, R_1 represents a C_{1-6} alkyl group which may be substituted, a $C_{6,10}$ aryl group which may be substituted or a heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, having total ring-constituting atoms of 5-10 and being optionally substituted;

* When W represents a bond then n is 0 and R_1 represents a hydrogen atom or a C_{1-6} alkyl group,

R2 represents a hydrogen atom or a C_{1-6} alkyl group which may be substituted by an optionally substituted phenyl group; and

R3 represents a pyridyl ring optionally substituted by a C_{1-4} alkyl group, C_{1-4} alkoxy group or a halogen atom.

2. A pyrimidone derivative or a salt thereof, or the solvate thereof or the hydrate thereof according to claim 1, wherein R3 represents an unsubstituted 4-pyridyl group.

3. A pyrimidone derivative or a salt thereof, or the solvate thereof or the hydrate thereof according to claim 1 or 2, wherein W represents a sulfonyl group $-S(O)_2-$.

4. A pyrimidone derivative or a salt thereof, or the solvate thereof or the hydrate thereof according to claim 1 or 2, wherein W represents a carbonyl group $-C(O)-$.

5. A pyrimidone derivative which is selected from the group consisting of:
2-(4-(pyrid-2-yl-acetyl-amino))phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one,
2-(3-(phenylmethylsulfonylamino)phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one,
2-(4-(5'-methoxy-5'-oxo-valeryl-amino)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one,
2-(4-(5'-hydroxy-5'-oxo-valeryl-amino)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one,
2-(4-(5'-piperid-1-yl-5'-oxo-valeryl-amino)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one,
2-(4-(chloroacetyl-amino)phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one,
2-(4-(4'-methyl-piperazin-1-yl-acetyl-amino)phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one,
2-(4-(4'-methoxy-4'-oxo-butyryl-aminomethyl)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one, and
2-(4-(4'-hydroxy-4'-oxo-butyryl-aminomethyl)-phenyl)-6-(pyrid-4-yl)-pyrimidin-4-one
or a salts thereof, or a solvate thereof or a hydrate thereof.

6. A medicament comprising as an active ingredient a substance selected from the group consisting of a pyrimidone derivative according to claim 1.

7. A GSK3β inhibitor selected from the group of a pyrimidone derivative according to claim 1.

8. Use of a compound according to claim 1 for the preparation of a medicament for preventive and/or therapeutic treatment of a disease caused by abnormal GSK3β activity.

9. Use of a compound according to claim 1,2,3,4 or 5 for the preparation of a medicament for preventive and/or therapeutic treatment of a neurodegenerative disease.

10. Use of a compound according to claim 9, wherein the neurodegenerative disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, tauopathies, vascular dementia; acute stroke,

traumatic injuries; cerebrovascular accidents, brain cord trauma, spinal cord trauma; peripheral neuropathies; retinopathies or glaucoma.

11. Use of a compound according to claim 1,2,3,4 or 5 for the preparation of a medicament for preventive and/or therapeutic treatment of non-insulin dependent diabetes; obesity; manic depressive illness; schizophrenia; alopecia; or cancers.

12. Use according to claim 11 wherein cancer is breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia or virus-induced tumors.

INTERNATIONAL SEARCH REPORT

Inter. Application No
PCT/EP 01/03637

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/04 C07D401/14 A61K31/506 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 24782 A (AMGEN) 11 June 1998 (1998-06-11) cited in the application page 0; claims	1,2,4,6
A	CHEMICAL ABSTRACTS, vol. 83, no. 28, 1975 Columbus, Ohio, US; abstract no. 10127z, page 853; column 2; XP002145638 abstract & JP 07 435633 A (MORI,H.) 25 September 1974 (1974-09-25)	1,2,6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 June 2001	05/07/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Francois, J

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